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pacemaker signals to the epicardial surface through said electrode pairs, to alter the effective refractory period in the heart, wherein the electrode pairs are arranged in two columns with one electrode in each pair in one column, and the other electrode in each pair in the other column.

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60. (Amended) A device for treating a heart to induce ion channel remodeling comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and for delivering periodic pacemaker signals to the epicardial surface through said electrode pairs, to induce ion channel remodeling in the heart, wherein the electrode pairs are arranged in two columns with one electrode in each pair in one column, and the other electrode in each pair in the other column.

Remarks

Reconsideration and allowance in view of the amendments made and comments which follow are respectfully requested.

Claims 12, 31, 50, and 58-60 are being amended. Claims 1-60 are now pending. Support for the amendments to claims 12, 31, 50, and 58-60 may be found in the specification at, *inter alia*, page 10, line 16 and page 11, line 20. The remaining changes to the claims merely introduce additional grammatical and format changes. Applicants maintain that these amendments raise no issue of new matter. An annotated version of amended claims showing all changes relative to the previous version of that claim is attached hereto as **Exhibit A**. Upon entry of the present Amendment, claims 1-60 will be pending and under examination in the subject application.

The Claimed Invention

The presently claimed invention provides a novel device and method which remodels gap junctions and ion channels, and alters the effective refractory period of the heart. The novel device according to the invention consists of two columns of linked multiple electrode pairs and a pacemaker which delivers periodic electrical signals to the heart to induce changes in cardiac expression and cardiac physiology. The presently claimed invention also provides novel methods to achieve the above-described changes.

Claim Objections

The Examiner objected to claims 58, 59, and 60 because of the following informalities:

- In claim 58, line 3, "of heart" should be --of a heart--,
- In claim 59, line 4, "of heart" should be --of a heart--,and
- In claim 60, line 3, "of heart" should be --of a heart--.

Applicants have amended claims 58-60 without prejudice by inserting "a" to state "of a heart", thereby rendering moot the Examiner's objections.

Rejections Under 35 U.S.C. §102

The Examiner rejected claims 1, 2, 9-13, 20-21, 28-32, 39-40 and 47-51 under 35 U.S.C. §102(e) as being allegedly anticipated by Knisley (U.S. Patent No. 5,824,028).

The Examiner stated that applicants state Knisley does not disclose signals:

- in the form of periodic electrical signal, or

- delivered through the use of electrode pairs.

The Examiner stated that Knisley discloses alternate leads and electrode combinations to provide variation in the polarity, timing and/or waveform shape (column 3, lines 23-34). The Examiner stated that variations in timing is read to be periodic electrical signals. The Examiner further stated that periodic signal is also disclosed in the Abstract as pacing (line 12) and that Knisley discloses an electrode, pair (column 3, lines 23-26).

The Examiner stated that applicants state Knisley does not disclose that gap junctions will be remodeled. The Examiner stated that the invention disclosed by Knisley <u>is understood</u> to remodel the gap junctions as indicated by:

- the recognition that "effects on stimulation result from changes in transmembrane ion channels" (column 1, lines 19-23); the <u>junction gaps are read to be the transmembrane ion channels</u>, and

- the recognition that "effects on stimulation" "result from changes in transmembrane ion channels" (column 1, lines 19-23), hence the gap junctions are being remodeled.

The Examiner stated that applicants state Knisley does not disclose that effective refractory period will be altered. The invention disclosed by Knisley <u>is understood to alter</u> the effective refractory period as indicated by recognition that the "transmembrane voltage" <u>changes "the state of transmembrane voltage-dependent ion channels that produce excitation or graded response"</u> (column 1, lines 28-32). The Examiner further stated that a graded response is understood to be a refractory period and that refractory tissue is also disclosed (column 3, lines 35-49).

The Examiner stated that claims 1, 10-12, 20, 29-31, 39 and 47-50 stand rejected under U.S.C. §102(b) as being allegedly anticipated by Kroll et al. (U.S. Patent No. 5,366,485) for the reasons of record.

The Examiner stated that applicants state Kroll et al. does not mention or suggest remodeling gap junctions. The Examiner stated that the invention disclosed by Kroll et al. impacts the heart cell function by defibrillation and that the impact on the heart cell function includes alteration of the "sodium channels." The Examiner further stated that "sodium channels" are understood as the gap junctions. Hence, the Examiner stated, changing or remodeling the gap junctions is disclosed (column 4, line 46 - column 5, line 45).

The Examiner stated that applicants state Kroll et al. expressly teaches away from using linked multiple electrode pairs. The Examiner stated that the invention disclosed by Kroll et al. teaches the uses of large surface area electrodes, understood to contain linked multiple electrode pairs (column 7, lines 43-47).

The Examiner stated that applicants state Kroll et al. does not teach or suggest altering the effective refractory period of the heart. The Examiner stated that the invention disclosed by Kroll et al. teaches that defibrillation impacts the refractory time and refractory period; during the refractory period, the cell is incapable of responding to another stimulus (column 5, lines 36-45).

In response, applicants respectfully traverse the Examiner's rejections.

A Gap Junction Is Not an Ion Channel

The Examiner asserts in this Office Action (as well as the prior Office Action) that a gap junction is an ion channel. Applicants respectfully disagree. Applicants attach hereto excerpts from

Lodish, H.F., Baltimore D., Berk A., Zipursky S.L., Matsudaira P. and Darnell J. (1995) *Molecular Cell Biology*. (3rd ed) New York, W.H. Freeman & Co. ("Darnell") as **Exhibit B**, which show unequivocally that an ion channel is not a gap junction.

An ion channel is a transmembrane channel for ions to cross a lipid bilayer down their electrochemical gradients. Ion channels transport only ions. Ion channels may be permanently open, voltage gated, or ligand gated. Ion channels which control cell membrane potential are generally exposed to the extracellular aqueous milieu as well as the cytosol of a cell. Even symporters and certain antiporters which cotransport ions with other molecules, are not ion channels (Darnell at page 640, second column, first full paragraph: "ion channels, ion pumps, and some antiporters transport only ions," emphasis added). Thus, a prerequisite for all ion channels is that they transport only ions — and thus the name ion channel.

In contrast to an ion channel, a gap junction is a junction between two cells consisting of a pore that allows the passage of molecules up to about 1200-2000 kD. Each pore is formed by an hexagonal array (connexon) of six transmembrane proteins (connexins) in each plasma membrane: when mated together the pores open, allowing communication and the interchange of metabolites between cells. As stated, molecules (usually below 1200 kD in human) may flow freely from cell to adjacent cell. While this may include ions — since ions are generally below the 1200 kD limit (Darnell at page 1158, first column, first full paragraph), gap junctions are not ion channels, just as symporters are not ion channels. Gap junctions are not specific for the transport of only ions; gap junctions are not specific for ions to cross a lipid bilayer down electrochemical gradients; and gap junctions are not exposed to the extracellular aqueous milieu and therefore are not voltage-dependent ion channels.

Gap junctions strictly connect the cytosols of adjacent cells. In view of the foregoing cited authority and remarks, one of ordinary skill in the art would not think of a gap junction as an ion channel, as the term ion channel is used, and would thus not interpret the term "ion channel" to include a gap junction.

A Graded Response Is the Not the Same as a Refractory Period

The Knisley reference cited by the Examiner states, "The transmembrane voltage change produced by and during a stimulation pulse (ΔV_m) is thought to be responsible for the effects of stimulation by changing the states of transmembrane voltage-dependent ion channels that induce excitation or a graded response."

The Examiner interprets the term "graded responses" in Knisley to mean refractory period. Applicants respectfully disagree. The meaning of the "graded responses" in Knisley is unclear, but whatever it could mean, it certainly doesn't mean refractory period. To the extent that "graded responses" may mean the magnitude of the signal which varies with the varying ionic currents (see *Darnell* at pages 640-644), the "graded responses" referred to in Knisley might refer to whether the voltage-dependent ion channels induced activation of the cell.

In contrast, a refractory period refers to the period after activation (or excitation) of a cell, in which the cell repolarizes itself so that another potential may be initiated — no activation nor excitation responses can occur during this period. A refractory period cannot be understood to be a graded response, since no response to an excitation stimulus from a cell during the refractory would be forthcoming. Therefore, the graded response in Knisley cannot be a refractory period.

To the extent that the passage in Knisley at column 1, lines 28-32, might be referring to a fundamental principle of electrical potential propagation caused by cellular activation induced by a stimulus, the term still does not refer to refractory period. In this scenario, a stimulus is first applied. Second, the transmembrane voltage-dependent ion channels open. Some of the transmembrane voltage-dependent ion channels may be at threshold stimulation or below (sub-threshold). Hence, not all voltage gated ion channels may open at the same instant. This phenomenon Knisley could be referring to as the "states of transmembrane voltage-dependant ion channels that induce excitation or a graded response." Thus, the response from the stimulus may achieve excitation or a graded response. The opening of ion channels (causing ions to flow into or out of the cell) changes the plasma transmembrane potential of the cell, since releasing or intaking ions makes the intracellular environment more or less charged than the extracellular environment. This difference in charge between the intracellular and extracellular environment yields a net charge at the plasma transmembrane (see *Darnell* at pages 640-644).

Neither Kroll et al. nor Knisley Teach altering an Effective Refractory Period of a Heart, but Only Relate at Most to a Refractory Period of a Cell

The Examiner asserts that Kroll et al. discloses that defibrillation impacts refractory period of a cell and that Knisley teach an effective refractory period since it mentions a refractory period. Applicants maintain that neither Kroll et al. nor Knisley teach or suggest altering an effective refractory period of a heart. The presently claimed invention provides a method to alter the effective refractory period of a heart, distinct from impacting the refractory period of a cell.

Applicants attach hereto as **Exhibit C**, Hoffman B. F. and Cranefield P.F. (1960) *Electrophysiology of the Heart* (pages 252-256). New York: McGraw-Hill Book Co. ("Hoffman"), which shows that a refractory period is distinctly different from an effective refractory period (see page 252, paragraph 1). Firstly, effective refractory periods applies to the heart and not to a single cell (page 252, paragraph 3 to top of page 253). Hoffman in referring to the heart, defines an effective refractory period as "the period which ends at the earliest moment during recovery when a response to a stimulus is conducted throughout the muscle" (page 253, paragraph 2). Hoffman further states that, "an effective refractory period ends at the moment when it becomes possible to evoke a new propagated response by an electrical stimulus. Such a response can be evoked only by a strong stimulus and appears only after considerable latency." This latency refers to when there is no signaling in the heart. Thus, an effective refractory period is not a refractory period.

Secondly, a heart is an organ and not a cell. And, by the definition of an organ, a heart is made up of a plurality of cells (excitable and non-excitable), extracellular matrices and tissues. Hence, phenomenons applicable to a cell cannot be presumed to apply to an organ. Since neither Kroll et al. nor Knisley teach altering the effective refractory period of a heart but relate only to a refractory period of a cell, applicants respectfully request that this ground of rejection be withdrawn.

Large Surface Area Electrodes of Kroll et al. Are Not Linked Multiple Electrode Pairs Consisting of Two Columns

Applicants respectfully disagree that the use of large surface area electrodes in Kroll et al. is understood to contain linked multiple electrode pairs (column 7, lines 43-47). The large surface area

electrodes from Kroll et al. are not linked multiple electrode pairs consisting of two columns used in conjunction with a periodic pacemaker electrical signal. In fact, nowhere in Kroll et al. are linked multiple electrode pairs consisting of two columns used in conjunction with a periodic pacemaker suggested or implied. Thus, the Kroll et al. does not teach or suggest the presently claimed invention.

<u>Summary of Applicants' Response to 35 U.S.C. §102 Rejections</u>

Knisley does not anticipate the presently claimed invention because:

1) Gap junctions are not ion channels;

2) Knisley only refers to voltage gated ion channels and not to gap junctions;

3) The refractory periods referred to in Knisley are not the effective refractory periods of the presently claimed invention.

Kroll et al. does not anticipate the presently claimed invention because:

1) Kroll et al. relates to large surface area electrodes and not linked multiple electrode pairs consisting of two columns;

2) Kroll et al. refers to sodium ion channels and not gap junctions;

3) The refractory periods referred to in Kroll et al. are not the effective refractory periods of the presently claimed invention.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 3, 7-8, 14, 17-19, 22, 26-27, 33, 36-38, 41, 45-46, 52, and 55-57 stand under 35 U.S.C. §103 (a) as being allegedly unpatentable over Knisley in view of Dahl et al. (U.S. Patent No. 5,203,348) for the reasons of record.

The Examiner stated that applicants state that there is no motivation to combine Knisley, Dahl et al., and Ideker (U.S. Patent No. 5,873,896). The Examiner stated that all three inventions are epicardial leads, Knisley (column 2, lines 31-35), Dahl et al. (column 4, lines 20-25), and Ideker (column 1, lines 45-49), and hence one skilled in the art would be motivated to combine these references.

The Examiner rejected claims 58-60 are under 35 U.S.C. §103(a) as being unpatentable over Knisley (U.S. Patent No. 5,824,028) in view of Ideker (U.S. Patent No. 5,873,893). The Examiner stated that Knisley discloses a method and device with electrode(s) oriented relative to cardiac fiber direction whereby the stimulation pulse reduces the non-uniformity of the transmembrane voltage change associated with arrhythmic conditions. The Examiner stated that the invention includes an electrical pulse generator (26), a lead assembly (25), and a plurality of electrodes (12). The Examiner stated that this invention focuses on the transmembrane potential and ion channels (column 1, lines 11-54) and recognizes the impact of treatment on the refractory tissue (column 3, lines 35-49).

The Examiner stated that this invention is understood to impact junction gap remodeling as indicated by the recognition that "effects on stimulation" "result from changes in transmembrane ion channels" (column 1, lines 19-23). The Examiner stated that the junction gaps are read to be the transmembrane ion channels.

The Examiner further stated that the invention is understood to alter the effective refractory period as indicated by the recognition that "transmembrane voltage" changes "the state of transmembrane voltage-dependent ion channels that produce excitation or graded response" (column 1, line 28-32); and that a graded response is understood to be a refractory period.

The Examiner stated that this invention is understood to induce ion channel remodeling as indicated by the recognition that "effects on stimulation" "result from changes in transmembrane ion channels" (column 1, lines 19-23), hence the ion channels are being remodeled. The Examiner stated that the electrode can be inserted in the myocardium, positioned to contract the epicardium or endocardium, or be a flat ribbon (column 2, lines 31-46). The Examiner stated that sutures (column 2, line 66 - column 3, line 2) can attach the electrode. The Examiner stated that alternate leads and electrode combinations are discussed to provide variation in the polarity, timing and/or waveform shape (column 3, lines 23-34); variations in timing is read to be periodic electrical signals. The Examiner stated that Knisley discloses the claimed invention except for disclosing the electrode pairs are arranged in two columns, with one electrode in each pair in one column, and the other electrode in each pair in the other column.

The Examiner stated that Ideker discloses a cardiac device for reducing arrhythmia and teaches that it is known to use an electrode configuration of an elongated primary strip having a plurality of electrodes positioned at spaced intervals, e.g. 1-4 millimeters (column 3, lines 2-4), along its length. The Examiner stated that Figure 5 shows electrodes mounted on a substrate, and that a column of electrodes are read to be the line of electrodes perpendicular to the long edge of strips 12 and 50, and the pairs are read to be the

electrodes side-by side on strips 12 and 50.

The Examiner stated that it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the electrode as taught by Knisley device, with the elongated primary strip as taught by Ideker. The Examiner stated that one having ordinary skill in the art would have been motivated to make such a modification in electrode to gain a low energy level stimulation that causes the patient minimal discomfort (column 1, lines 63-67).

In response, applicants respectfully traverse the Examiner's rejections.

Without conceding the correctness of the Examiner's assertions but to expedite prosecution, applicants have hereinabove amended apparatus claims 12, 31 and 50 without prejudice, to recite an electrode "consisting of two columns." These amendments further distinguish the presently claimed apparatus from the cited prior art.

As was previously addressed: 1) gap junctions are not ion channels; 2) "graded responses" do not mean "refractory periods;" and 3) an "effective refractory period" is not the same as a "refractory period", nor can it be interpreted to be one. Therefore, applicants request that this ground of rejection be withdrawn.

Applicants maintain that the presently claimed invention is not obvious because: (1) one would not be motivated to combine the references proposed by the Examiner; and (2) even if the reference were combined, the combination does not suggest nor disclose the presently claimed invention. Applicants also maintain that an understanding of the purpose of the cited devices may aid in understanding the physical features of these devices, and why one

skilled in the art would not combine them.

Ideker Relates to a Single Pulse Electrode Device, Not a Periodic Pacemaker Device

The Ideker device is created specifically to prevent arrhythmia by preventing the propagation of an arrhythmic current. This is thought to be done by the Ideker device by shortening the critical mass of the myocardium involved in arrhythmia. The critical mass referred to in Ideker is the mass that is required for perpetuation of arrhythmia. Ideker states that below the critical mass required to perpetuate an arrhythmic signal, arrhythmia can not take place (see column 1, lines 21-23).

The Ideker device provides a sufficient pulse to hyperpolarize a line (or activation front) so that such line will not be hyperpolarized by an arrhythmic signal, thereby preventing and inhibiting arrhythmia. By energizing the electrode during arrhythmia with a pulse, Ideker intends that the electrode divides the myocardium into segments, each segment having the critical mass insufficient to maintain arrhythmia (column 1, lines 53-62). This, Ideker proposes, will prevent or reduce the likelihood of arrhythmia (column 1, lines 53-57). Therefore, the Ideker device is a single column electrode meant to produce a single line of response with a single pulse. The electrical pulse in Ideker is meant to be sustained for at least 30 seconds, which is thought by Ideker to be a sufficient time to inhibit the spread of an arrhythmic action potential (column 3, lines 25-28). The specification at column 3, line 35-50 of Ideker reads, "In operation, during arrhythmia...the device **10** creates a line of hyperpolarized heart tissue such that cardiac electrical conductance across the hyperpolarized line of tissue is prevented." Here, Ideker does not disclose use of a periodic pacemaker pulse. It is clear

from the Ideker specification that a single pulse is to be used to create a line (or an activated front) of heart tissue to prevent arrhythmia.

Further, the pairs of electrodes to which the Examiner refers in Ideker are two separate electrodes , a primary and secondary, which provide differing pulses (column 2, lines 22-25). The secondary (pair) electrodes function entirely different from the primary electrode (which is used to create the line or the activated front). Indeed, the second electrode produces some electrical pulse, but the pulse produced by the second electrode is used not to hyperpolarize all the tissue immediately beneath the electrode, but instead is used to act as a buffer (by hyperpolaizing and simultaneously depolarizing) for the primary electrode (column 2, lines 22-25 an column 4, lines 12-28). That is, the secondary strip of electrode is used to stop the spread of an activation current created by the primary electrode. No pacemaker function is presented, and it would be contrary to Ideker to use a pacemaker periodic signal. Thus, Ideker teaches away from the presently claimed invention.

Knisley Relates to a Single Pulse Device, Not a Periodic Pacemaker Device

The Examiner asserts that Knisley discloses ultimate leads to an electrode combination to provide variation in polarity, timing, and or waveform shapes. Here, the Examiner reads timing to be a periodic electrical signal. Applicants respectfully disagree with this assertion. The term "timing" referred to in this passage does not refer to a periodic pacemaker pulse from a pulse generator, but instead refers to the length of time in which it takes to hyperpolarize and repolarize an excited cell. Hence, Knisley does not disclose a periodic electrical signal. The device in Knisley is

meant to abrogate an arrhythmia by applying a single stimulation pulse to the heart, the pulse being of sufficient magnitude to disrupt arrhythmia — and not by periodic pacemaker electrical signals (see column 1, lines 57-61). Thus, Knisley teaches away from the presently claimed invention.

The Proposed Combination of Knisley and Ideker Does Not Provide the Invention

The proposed combination of Knisley and Ideker would not provide the presently claimed invention, since both Knisley and Ideker are directed to single pulse devices to be used for the immediate abrogation of an arrhythmic action potential, and not periodic pacemaker signals, which are recited in applicants' method claims. Further, applicants apparatus claims recite linked multiple electrode pairs consisting of two columns, and neither reference shows this feature. Hence, the references, even if combined, do not render obvious but rather teach away from the presently claimed invention.

The Dahl Defibrillation Conductive Electrode Segment Does Not Teach or Suggest Linked Multiple Electrodes with a Pacemaker

The Dahl reference relates to apparatus defibrillation electrode segments with large effective surface areas and lower electrical impedance at or near the electrodes (column 2, lines 9-13). The Dahl device provides defibrillation electrode structures with a relatively large size while reducing the non-uniform field distribution (column 2, lines 18-22). The Dahl defibrillation electrode segments are "a single metal wire, a plurality of wires in a braided or twisted configuration, helically wound coils, or a woven mesh or a woven screen"(column 3, lines 30-33) used to contact the heart and create a large effective surface area. Therefore, the Dahl electrode segments are not linked multiple electrode pairs consisting of two

columns. Further, the Dahl device does not provide a pacemaker for delivering a periodic pacemaker electrical signal.

The Proposed Combination of Knisley and Dahl Does Not Provide the Presently Claimed Invention

As discussed above, Knisley relates to a single pulse device for the abrogation of arrhythmia and Dahl et al. relates to large surface area defibrillation electrode segments.

Neither Knisley or Dahl et al. teach or suggest linked multiple electrode pairs consisting of two columns and periodic pacemaker electrical signals for altering the effective refractory period of the heart, gap junction remodeling and ion channel remodeling. Even if one were to combine Knisley and Dahl et al., the presently claimed invention would not be obvious, since as mentioned, neither reference provides an apparatus with a periodic pacemaker electrical signal or linked multiple electrode pairs consisting of two columns. Therefore, Knisley and Dahl et al., even if combined, do not render obvious the presently claimed invention.

Conclusion

In view of the foregoing, applicants urge that the present rejections be withdrawn, and that all of the pending claims 1-60 be allowed.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invites the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this

Response. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents, Washington, D.C. 20231.

9/17/01

Peter J. Phillips — Date

Reg. No. 29,691

Applicants: Michael R. Rosen, et al.
Serial No.: 09/505,458
Filed: February 11, 2000
page 1

AMENDMENT TO CLAIMS 12, 31, 50, 58-60 UNDER 37 CFR § 1.121(b) OF THE PREVIOUS VERSION

In The Claims

12. A device for treating a heart to obtain gap [junctional] junction remodeling, comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and a pacemaker for delivering periodic pacemaker electrical signals to the epicardial surface through said electrode pairs, to remodel gap junctions in the heart.

31. A device for treating a heart to alter the effective refractory period, comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and a pacemaker for delivering periodic pacemaker electrical signals to the epicardial surface through said electrode pairs, to alter the effective refractory period in the heart.

50. A device for treating a heart to induce ion channel remodeling, comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and a, pacemaker for delivering periodic pacemaker electrical signals to the epicardial surface through said electrode pairs, to induce ion channel remodeling in the heart.

58. A device for treating a heart to obtain gap [junctional] junction remodeling, comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and for delivering periodic pacemaker signals to the epicardial surface through said electrode pairs, to remodel gap junctions in the heart, wherein the electrode pairs are arranged in two columns with one electrode in each pair in one column, and the other electrode in each pair in the other column.

59. A device for treating a heart to alter the effective refractory period comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and for delivering periodic pacemaker signals to the epicardial surface through said electrode pairs, to alter the effective refractory period in the heart, wherein the electrode pairs are arranged in two columns with one electrode in each pair in one column, and the other electrode in each pair in the other column.

60. A device for treating a heart to induce ion channel remodeling comprising a substrate having linked multiple electrode pairs consisting of two columns for contacting an epicardial surface of a heart and for delivering periodic pacemaker signals to the epicardial surface through said electrode pairs, to induce ion channel remodeling in the heart, wherein the electrode pairs are arranged in two columns with one electrode in each pair in one